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JPRS: 4313

6 January 1961

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CLINICAL OBSERVATIONS ON THE EFFECT OF RESPERINE ON
THE CORONARY CIRCULATION OF HYPERTENSION PATIENTS

-USSR-

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FOREWORD

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CLINICAL OBSERVATIONS ON THE EFFECT OF RESERPINE ON THE
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Following is the translation of an article by Prof.
K. N. Zamyslova and V. Ya. Yurazh (Moscow) in
Klinicheskaya Meditsina, Vol. 38, No. 9, Moscow
1960, pages 90-95/

Preparations from the alkaloids of *Rauwolfia serpentina* have only lately, since 1954, been introduced into the practice in the treatment of hypertension. They have met very quickly with wide recognition and there is already a great amount of literature on the study of their action. All the authors, native and foreign, who have used reserpine and other preparations in the clinic, recognize their great practical value. They are indicated in almost all stages of hypertension and for almost all sufferers from this ailment.

In the earlier stages it is usually quite sufficient to prescribe reserpine alone to obtain a good hypotensive effect; very often this effect is obtained from small doses of the drug as a result of a course of treatment given under ambulatory conditions. Not infrequently, as we may judge from the data of the Institute of Therapy of the Academy of Medical Sciences of the USSR, a good effect from the use of reserpine is observed in patients with a stable form of hypertension, in stages II and III of hypertension, and also in secondary hypertension. The prescription of reserpine is indicated even in cases of a malignant course, when the necessity later inevitably arises of changing to an integrated treatment. It is well known that the *Rauwolfia* preparations are prescribed in individual, initially small doses, which often require subsequent augmentation; they possess mild cumulative properties; the hypotensive action manifests itself more often at the end of the second week of use of the drug; and the courses of treatment and maintenance of the hypotensive effect must be lengthy. If one does not succeed in bringing about a substantial lowering of the arterial pressure through the use of reserpine alone, it is often found very helpful in combination with ganglion-blocking drugs, since

it intensifies the hypotensive action of the latter, permits their dosage to be reduced, limits extraordinary fluctuations of the arterial pressure caused by the ganglion-blocking drugs and mitigates the side phenomena caused by them.

N. A. Ratner and Yu. D. Vadkovskaya have shown in their investigations that the blood flow in the kidneys is considerably increased under the effect of reserpine, in many cases reaching the normal level; the filtering function of the kidneys is also improved. Analogous data have been obtained by S. K. Kiseleva.

Thus, there remains no doubt that the *Rauwolfia* preparations are valuable drugs for the treatment of hypertension patients.

The mechanism of the action of reserpine and allied alkaloids has not been fully studied. Reserpine is credited above all with action on the central nervous system. The hypothalamic region and the prehypothalamic conducting passages are recognized as the main place of application of its action. In the opinion of reserarchers, it has a braking effect upon the sympathetic centers and causes a depression of sympathetic predominance; hence its sympatholytic effect, the lowering of the vasomotor pressor activity, the antihypertensive effect and activation of the parasympathetic section of the vegetative nervous system. A peripheral sympatholytic action, apparently directly on the vessels, is also recognized.

Practically, the *Rauwolfia* alkaloids exert a sedative and hypotensive action. This combination of properties is essentially pathogenetic and hence is known to be helpful to hypertension patients.

Because of its vagotonic action, reserpine often causes bradycardia, sometimes pronounced - down to 40-50 beats a minute. This slowing down of the rythm of the heart contractions is helpful under specific conditions, for example in deficient blood circulation in hypertension patients; in these cases the restoration of compensation, caused primarily by the lowering of the arterial pressure and to a considerable extent precisely by the retardation of the rythm, not infrequently sets in under the influence of reserpine. This positive action of reserpine, and, all the more, its combination with ganglion-blocking drugs, is often observed without any application of cardiac glucosides; in case of the necessity of combination with the latter, the effect from the action of cardiac glucosides is accelerated and intensified to a considerable extent. Cases have been described of the

disappearance of paroxysmal tachycardia upon the administration of reserpine.

Rauwolfia preparations possess a certain amount of accumulation and distinct side action. The latter may express itself in the appearance of sluggishness, weakness, sleepiness; the raising of the activity of the vagus accounts for a swelling of the mucous membranes of the nose and pharynx, an increase in the secretion of gastric juice, rarely vomiting and diarrhea. There are descriptions of individual cases of the activation of a peptic ulcer, bronchial asthma or gall stones. Manifestations of the side action of reserpine are comparatively rare, and usually not serious. They are observed only at the beginning of treatment, often die out independently, are easily relieved with atropine and almost never reach a degree requiring a reduction of the dose or a discontinuing of the treatment.

The appearance of profound nervous depression or even an indication of such a condition in the past are considered the only serious contra-indications to the prescription of reserpine.

Naturally, the question of the effect of reserpine on coronary circulation attracts special attention. As stated above, one of the aspects of the action of reserpine is the relative rise in the tonus of the vagus. This situation is a definite warning; it allows one to admit the possibility of an unfavorable action of the preparation on the coronary circulation, and especially in cases where it is known to be disturbed.

In talks at congresses and meetings of the Therapeutic Society, certain clinicians have pointed out the unfavorable action of reserpine on coronary circulation. To be sure, these were verbal statements; no statistics or concrete examples were cited that could be subjected to evaluation. However, so far as is known to us, these fears have found a wide response among the mass of physicians. An article by V. N. Dyachenko (of the clinic directed by N. Ye. Kavetskiy) published at the end of 1958 utters such a warning; it is expressed in the final point of the conclusions in the following words: "The presence of coronary sclerosis is a contra-indication to the use of reserpine." It should be pointed out that the factual data adduced by the author do not orient the reader toward a strict fulfillment of this recommendation. Thus, in 93 (81.5%) out of 114 patients, a good effect was obtained from treatment with reserpine. In 18 of them there were, before treatment, pains in the region of the heart and certain changes in the electro-

cardiogram; upon administration of reserpine to 12 patients "unpleasant feelings occurred in the region of the heart", which passed away when the dose of reserpine was reduced. Consequently, the author's warning, though serious in content, is not commensurate with the insignificant symptoms which he observed.

We are deeply convinced that the exaggeration of the danger of the use of reserpine is more harmful than the objective evaluation of all its positive and negative qualities. If one takes the point of view that administration of Rauwolfia is contra-indicated in the presence of coronary atherosclerosis, this will result in a sharp narrowing of the circle of patients to whom it can be prescribed. Indeed, clinical experience is convincing us more and more that hypertension and atherosclerosis are very frequently combined; this applies all the more to elderly people, where there are the late stages of hypertension in its protracted course. This combination of the two forms of disease is encountered so often and a number of main pathologic manifestations coincide so regularly that it is precisely this that has served A. L. Myasnikov as a basis for offering for consideration a new conception, recognizing the existence of a single disease manifesting itself simultaneously or successively by this or that syndrome.

At the same time, in accordance with the model plan for hypertension treatment worked out by the Institute of Therapy of the Ac. of Med. Sc. of the USSR, energetically acting hypotensive drugs are already being used in later stages, and this applies in the overwhelming majority of cases both to the more advanced age of the patients and to the more protracted course of the disease, i.e. precisely to those cases in which the combination of the two disease conditions (or perhaps syndromes) is known to be almost invariable.

We have observed 400 patients who have received reserpine in the clinical department of the Institute. A. V. Kolosov, N. K. Belyayeva and S. I. Bitkova have treated 180 patients with reserpine in the polyclinical department.

In 177 out of the 400 patients observed by us there was a combination of hypertension with coronary atherosclerosis, which manifested itself clinically by attacks of stenocardia (see table); the presence of atherosclerosis was confirmed in all cases by special investigations (electrocardiography, ballisto-cardiography, roentgenokymography of the pectoral aorta, roentgenography of the abdominal aorta, rate of spread of the pulse wave, lipide

content in the blood, etc.). All the patients of this group were over 40 years of age; their hypertension was in stages II or III.

In 223 patients, no clinical signs of atherosclerosis were established; however, 60% of them were over 40 years of age and the overwhelming majority belonged to stage II of hypertension. Not one of them had typical attacks of stenocardia; however, nearly all the elderly patients and half the young ones complained about one or another unpleasant or painful feeling in the region of the heart having definite dynamics in the process of treatment, which we took into account.

Effect of reserpine on coronary circulation in
hypertension patients

Diagnosis

Result of treatment	coronary atherosclerosis, stenocardia		hypertension without signs of coronary sclerosis.	
	number of patients	in %	number of patients	in %
Improvement	59	33	--	--
No improvement	93	53	212	96
Worsening	25	14	11	4
Total	177		223	

The patients of both groups went through more or less protracted courses of treatment with reserpine, most often for 3-4 weeks, sometimes up to 7 or 8 weeks. The patients who were given polyclinical treatment received reserpine continuously for 1-1½ years, usually in small doses, to maintain the hypotensive effect obtained at the beginning of the course of treatment. Depending upon the degree and stage of hypertension, various doses of reserpine were prescribed, most often 1-1.5 mg a day; in certain cases the doses had to be increased to 2-2.5 mg or even 3 mg a day.

Before taking up the question of the action of reserpine on the coronary circulation, we consider it necessary to emphasize once more that according to our data reserpine in a large percentage of cases produces a considerable hypotensive effect. In 83% out of 400 patients there was an improvement, with a considerable lowering of

the arterial pressure; in 37%, the pressure dropped to normal; the majority of this group had stage II of hypertension and 22 even stage III. Only in 73 patients (17%) was the hypotensive effect small, chiefly in stage III of the disease. According to the data of A. V. Kolosov, N. K. Belyayeva and S. I. Bitkova, a positive effect was obtained in 92% of the polyclinical cases. There are similar indications as to the positive action of reserpine in many native and foreign authors.

As stated above, the larger part of the patients (223) had no typical attacks of stenocardia; only in 11 of them did the administration of reserpine cause a certain intensification of unclear, untypical pains, but not one of the large group of patients had attacks of stenocardia. In 5 patients, however, the electrocardiogram indices were worse; this was expressed in a lowering and flattening of serration T, the appearance of a negative T, a change in the interval S-T. The use of euphylline eliminated these changes.

In another group of patients (177) treatment with reserpine was undertaken in the presence of undoubted coronary atherosclerosis, which manifested itself primarily in attacks of stenocardia. In 93 of them, neither the subjective condition nor the electrocardiogram indices were changed; in 59, against the background of treatment with reserpine, the attacks of stenocardia abated; in 20, the electrocardiogram improved, as expressed in the positive dynamics of serration T and in the normalization of the interval S-T.

In 25 patients (14%) the stenocardia attacks became more frequent, and in 8 the electrocardiogram indices worsened. Prescription of diuretic or euphylline without changing or even reducing the reserpine dose rapidly eliminated the impairment in all these cases; the course of treatment was continued, and the hypotensive effect was usually insured. In many cases in the presence of frequent attacks of stenocardia reserpine was already prescribed at the very beginning of the course together with theobromine preparations; in not a single one of these cases were the stenocardia attacks observed to become more frequent. In not a single instance of the use of reserpine did we observe grave complications in the form of focal disturbances of the coronary circulation.

An analysis of those cases in which an increase in the frequency of stenocardia attacks was observed showed that this deterioration occurred only with administration of large doses of reserpine (without euphylline) or when the arterial pressure dropped rapidly and sharply. It

is the latter circumstance, to judge from our data, that is the main cause of a possible deterioration of the blood supply to the myocardium. But this cause can be removed without difficulty: one needs only to dose the medicine carefully and watch attentively the rate and degree of the drop in arterial pressure.

In looking through the rather large amount of literature concerning the use of Rauwolfia preparations, we have nowhere encountered indications of serious complications on the part of the coronary circulation that could be ascribed to the negative action of these drugs (Page, Pickering, Smirk, Schroeder, McQueen). In a review article on the treatment of hypertension by serpasil, I.I. Veretyanov says that he has not found in the literature any indications of serious complications from the use of Rauwolfia. To the same effect are the published data of A. V. Kolosov and co-authors; Kh. Kh. Kibarksis and I. G. Stupelis; N. I. Guseva; K. A. Trotsenko; G. A. Glezer; N. B. Ginzburg and N. M. Ter-Avakova; S. K. Kiseleva. Together with our cases, this amounts to 1,140 observations by Soviet authors, who testify to the helpfulness of reserpine in hypertension, and to its pronounced hypotensive action; moreover, not one of the above-enumerated authors gives concrete indications of serious disturbances in its use on the part of the coronary circulation or any other complications that would oblige one to renounce the wide use of reserpine.

In accord with our data, concerning 59 patients, the article by N. B. Ginzburg and N. M. Ter-Avakova also stated that in a number of cases the lowering of the arterial pressure and the improvement of the general condition was accompanied by a reduction or cessation of the pains in the region of the heart.

One of the articles by American authors (Lewis, Lubin, January and Wild) is specially devoted to the treatment of angina pectoris with Rauwolfia. The authors describe, in 14 out of 15 coronary atherosclerosis patients with angina pectoris attacks, a good effect from treatment with reserpine alone, which the patients received for a long time, up to 10 months. Not a single case was observed, the authors emphasize, of infarct of the myocardium or decompensation. The authors attribute the positive effect to the sedative action of reserpine and the establishment, as they put it, of the "physiological balance" between the requirements of the myocardium and the coronary blood supply, which is improved thanks to the vessel-widening action of reserpine.

We are, of course, far from calling for the treatment of stenocardia especially with Rauwolfia preparations, the less so in the absence of a rise in arterial pressure; for this purpose we have at our disposal a sufficient number of medicaments and other medical measures, which in most cases relieve the patient's condition. But, in stressing the great practical value of reserpine, we have considered it important to clarify the effect of reserpine on the coronary circulation.

Still, recognizing the possibility of the vagotropic and sometimes excessive hypotensive action of reserpine, we consider it necessary to observe certain precautionary measures in prescribing the drug to hypertension patients suffering simultaneously from coronary atherosclerosis. These precautionary measures are very simple and should consist in the following: 1) do not begin treatment at once with large doses of reserpine; 2) in pronounced cases of coronary failure, do not bring the dosage up to the maximum in order to avoid the vagotropic action of reserpine; when the hypotensive effect from medium-sized doses is insufficient, change to a combination with ganglion-blocking drugs; 3) watch attentively the rate of decline in the arterial pressure and do not permit too rapid or sharp a drop, which may, indeed, have a negative effect on the blood supply to the myocardium, whose relative deficiency is peculiar to hypertension patients; 4) endeavor to lower the arterial pressure to the normal level: the latter may prove insufficient to insure a satisfactory blood supply to the myocardium; 5) in case of very slight symptoms of impairment of the coronary circulation and frequent stenocardia attacks, prescribe reserpine prophylactically from the very beginning of the course of treatment together with theobromine preparations or nitrites.

If these conditions are observed, there are no grounds for fearing negative reactions from the use of reserpine and there is no need to confine the indications to a wide use of this undoubtedly helpful drug even in cases with pronounced clinical symptoms of coronary failure.

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